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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/822,607 | 04/12/2004 | Xavier Paliard | PP01612.011 | 3674 |

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| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
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| 1648 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/822,607 | PALIARD ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *45-48 and 63-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-48, 63-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### RCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/26/2007 has been entered. The RCE follow:

### *Response to Amendment*

This is a response to the amendment filed on 06/26/07. Claim 45 has been amended. Claims 1-44 were canceled. Claims 45-65 are pending before the examiner. Claims 45-48 and 63-65 are considered before the examiner.

### *Priority*

(**Prior Objection Maintained**). The priority based on the effective filing date of the provisional Application No. 60,161,713 is still denied. The support pointed out by Applicants in the provisional Application 60,161,713 has been reviewed. However, the statement asserted by Applicants as the support of the claimed polynucleotide does not teach that the isolated polynucleotide encoding the HCV-1 antigen polypeptide of NS3NS4NS5ab and core as claims drafted. It only indicates that the isolated polynucleotide encoding the NS3NS4NS5ab fusion proteins.

Moreover, Applicants assert that the first passage of the page 4 explains the core is one of the products cleaved from the HCV polyprotein and the statement in the first and second paragraph use an open language of "comprises" to describe the fusion protein. The last sentence of the second paragraph states the polynucleotide can also comprise other nucleotide sequence. Therefore, Applicants concludes that it is clear that a fusion including core in addition to NS3 NS4 and NS5 was indeed intended.

While the last sentence of the second paragraph states the polynucleotide can also comprise other nucleotide sequence, it explicitly teaches that such sequence is the sequence encoding linkers, signal sequence, or ligands useful in protein purification such as glutathione-S-

transferase and staphylococcal protein A. Therefore, reading from the entire disclosure the paragraphs provided by Applicants or the entire provisional document, there is not implicitly or explicitly indicates that the isolated polynucleotide encoding the HCV fusion polypeptide should or would comprise the core antigen. The additional sequence should comprises in the polynucleotide is the fusion tag or linker useful for the recombination protein purification rather than an additional immunological concern.

In view of the lack of additional evidence to support the claimed polynucleotide comprising the HCV core polypeptide, the objection of the priority based on the effective filing date of provisional Application 60,161,713 is still maintained.

***Claim Rejections - 35 USC § 112***

The rejection of claims 45-48 and 63-65 under 112 1st paragraph are withdrawn necessitated by Applicants' amendment.

**New Ground Rejections:**

***Claim Rejections - 35 USC §103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 45-48 and 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houghton et al. (a) (US patent No. 5,683,864A1, "864" patent) or Houghton et al. (b) (US patent No. 6,312,889B1, "889" patent) or Houghton et al. (c) (WO91/15771A1, "771") .

3. The claims are directed to an isolated or purified polynucleotide or composition comprising said polynucleotide that encodes a fusion protein consisting essential of Hepatitis C virus polyproteins of the full length NS3 and NS4, an NS5a and NS5b and core protein.

4. The "864" or ""889" patent teaches a method how to make a fusion protein that comprises a region of the core protein, and a sequence from at least one of the NS3, NS4, S, and NS5 proteins (Abstract or Columns 2-3 and column 5 for the US patents and pages 3-4 and page 8 for ""771"), wherein the non-structural protein antigens can be the whole non-structural proteins as one immunological domain or an immunologically reactive fragment thereof. How such recombinant fusion protein can be constructed and produced are described in Column 5, line 25. Further, the reference teaches that NS5 antigen can be selected from the range consisting of amino acids 2000-3011 (claims 1-14 or examples 5 and 7). This referenced sequences comprises the portions of both the NS5a and the NS5b proteins. While the references do not precisely teach the polynucleotide construct encoding the fusion protein comprising the full-length NS4 fused with other non-structural proteins NS4 and NS5a/NS5b and core, the information provided by the patents teaches and suggests how to make such polynucleotide construct encoding such claimed fusion polyproteins of HCV (Example 7). The reference patents also concluded that "in similar manner for making all kind of such fusion proteins or modifications of the above-described modes for carrying out the invention that are obvious to those of skill in the fields of molecular biology, immunology and related fields (See last paragraph in column 20). Therefore, it would have been obvious for an ordinary skill in the art to be motivated for making a polynucleotide construct that encodes the fusion proteins comprising the HCV NS3 in full length fused with other non-structural proteins including NS4, NS5a and NS5b and structural protein of core antigen absence of any unexpected result.

5. Claims 45-48 and 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cho et al. (Vaccine 1999, Vol. 17, pp. 1136-1144) and Lagging et al. ( J. Virol. 1995, Vol. 69, No. 9, pp. 5859-5863) or Geissler et al. (J. Immunol. 1997, Vol. 159, pp. 5107-5113).

6. The claimed invention is directed an isolated polynucleotide or composition comprising the polynucleotide encoding the fusion protein consisting of HCV core, NS3-NS5ab, and pharmaceutical expectable excipient as well as an adjuvant.

7. Cho et al. disclose a plasmid DNA that encodes the non-structural polyprotein of HCV comprising NS3, NS4 and NS5 (pTV-NS345). Because the NS5 contains amino acid residues from 1019 to 3010 (See Fig. 1 on page 1139), it therefore, inherently comprises NS5a and NS5b.

The plasmids are constructed with or without a cytokine of GM-CSF (pTV-NS345/GMCSF, see fig. 1 on page 1139), when the plasmid DNA encoding the GM-CSF is administered together with the nucleotide sequence encoding the HCV polyprotein, the cytokine of GM-CSF is an adjuvant that enhances the immune response produced by HCV polynucleotide (See Table 2 on page 1140).

8. While Cho et al. do not teach to use HCV core antigen, HCV core antigen has been well studied to contain both T Cell and B cell immunological epitopes capable of inducing significant T cell (CTL and cytokine) and B cell humoral responses as evidenced by Geissler et al. (Figs. 1-4) and Lagging et al. (See Figs. 1-4 and Table 1). Because after testing several identified epitopes in HCV core antigen, they concluded that HCV core is a candidate antigen for developing the genetic vaccine to control the HCV infection (See Abstracts).

9. Therefore, it would have been obvious for any person skill in the art to be motivated for making a DNA vaccine composition comprising the polynucleotide sequences encoding both HCV structural core and non-structural NS345 antigens that are approved to induce an optimal level of immune responses against each of the HCV antigens. Therefore, absence of any unexpected result, the claimed invention as a whole is prima facie obvious absence unexpected results.

***Conclusion***

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Baoqun Li

BAOQUN LI, MD
PATENT EXAMINER

Bao Qun Li
August 30, 2007